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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 11/20/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,439	DOETSCH, VOLKER	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9-11,14-18,20-44 and 89-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 9-11, 14-18, 20-44, and 89-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 9/2/03 in Paper No. 14 is acknowledged and has been entered. Claims 5-8, 12, 13, 19, and 45-88 have been cancelled. Claims 1-3, 9, 10, 17, 18, 21, 24, 26-28, 32, 33, and 36-44 have been amended. Claims 89-91 have been added. Accordingly, claims 1-4, 9-11, 14-18, 20-44, and 89-91 are pending. Claims 1-4, 9-11, 14-18, 20-44, and 89-91 are under examination.

Oath/Declaration

2. The objection made to the Oath/Declaration has been withdrawn.

Rejections Withdrawn

Claim Rejections - 35 USC § 112

3. The rejections of claims 5-8, 12, 13, 19, and 45-88 are now moot in light of Applicant's cancellation of the claims.

4. In light of Applicant's amendment and argument, the rejection of claims 1-4, 9-11, 14-18, and 20-44 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 91 is vague and indefinite in reciting, "sufficient" because the term "sufficient" is a subjective term that lacks a comparative basis for defining its metes and bounds.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 90 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 90 recites that the intact biological compartment is not immobilized. This is a recitation of a negative limitation excluding immobilization of the biological compartment on a solid phase. However, the specification fails to provide teaching or disclosure for such recitation of negative limitation in the claims. The recitation is not supported by the instant specification, and does not flow from the specification and is

therefore considered to encompass new matter. See In re ANDERSON, 176 USPQ 331 (CCPA 1973).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1-4, 10, 11, 14, 17, 18, 22, 23, 26, 29-32, 33, 34, 38, 41-44, and 89-91 and rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al. (^{19}F NMR Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)) for reason of record and as follows.

Williams et al. teach extracting structural or conformational information from NMR data set for macromolecules, i.e. overexpressed proteins (glycolytic enzymes: hexokinase (HXK, 104 kDa), phosphoglycerate kinase (PGK, 45 kDa), and pyruvate kinase (PYK)) in an intact biological compartment, i.e. intact cell (yeast Saccharomyces cerevisiae), using ^{19}F NMR (NMR detectable nucleus) longitudinal relaxation time measurements to assess their rotational mobility in the intact cells. The enzymes in the cells are labeled by biosynthetic incorporation of 5-fluorotryptophan. Williams et al. specifically determine the extent of enzyme immobilization as the result of complexation (tight binding) to other cellular macromolecules by comparing their visibility of the ^{19}F

resonances in spectra of intact cells with that of disrupted cell preparations (see Abstract, page 490, column 2, and 497, column 1). The yeast cells were prepared by transformation with one of three plasmids by operably linking (insertion) the coding sequence for the yeast enzymes into LEU-2-expressing plasmid (pKV49) where they were under the control of a PGK promoter. This non-native promoter is constructed by replacing the PGK UAS with the GAL-4 dependent GAL1-10 UAS. Expression from this vector is allowed in the presence of galactose and absence of glucose; thus, can be regulated or inhibited by manipulation of the growth medium. Restriction fragments containing the coding sequence for the enzymes were inserted into the expression site of pKV49. Some cells were transformed using URA-3-containing plasmid, pUG41S. The transformed cells were incubated (grown) in a medium, induced, labeled, then set in a buffer suspension (see page 490, column 2 to page 491, column 1: Yeast transformation and enzyme induction and Cell immobilization and perfusion). For ^{19}F NMR measurement of the conformation (rotational mobility) of the proteins in vivo, Williams et al. teach contacting the cells with radio frequency using UnityPlus 400 MHz spectrometer to excite the ^{19}F NMR, wherein the resonant frequency of ^{19}F at this field is 376.29 MHz. Williams et al. teach collecting radio frequency data; thereby producing NMR data set so as to analyze structural information of the enzymes from the data set. Viscosity of the enzymes were also measured to be 2-fold greater than viscosity of pure water (see page 491, column 2, Figures 1 and 2, and page 496, column 1). Williams et al. suggest application of these measurement studies in measuring translational

diffusion coefficients of HXK and PGK in the cell using pulse field gradient techniques, which have been used with hemoglobin in human cell, i.e. erythrocytes.

8. Claims 1-4, 10, 11, 14-17, 21, 29, 32, 38-42, and 89-91 are rejected under 35 U.S.C. 102(a) as being anticipated by Serber et al. (High-Resolution Macromolecular NMR Spectroscopy Inside Living Cells, J. Am. Chem. Soc., 123: 2446-2447 (February 2001)).

Serber et al. teach using high-resolution In-cell NMR spectroscopy to provide conformational information, i.e. three dimensional structures, in the form of NMR spectra, of macromolecules such as overexpressed proteins, i.e. MerA, inside living bacterial cells (E. coli) (see page 2446, column 1). MerA, which is labeled with ^{15}N (NMR detectable nucleus), is first grown in unlabeled LB medium, then protein production is induced following transfer of bacteria into ^{15}N labeled minimal medium. After harvest, the cells are contacted with radio frequency to excite the ^{15}N label; thereafter, [^{15}N, ^{1}H]-HSQC spectral data is collected, and then analyzed using 500 MHz NMR spectrometer equipped with a 5 mm triple resonance cryoprobe (see page 2446, column 2 and Figure 1). Serber et al. suggest application of the method in eukaryotic yeast cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 27 and 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. (^{19}F NMR Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)) for reason of record.

10. Claims 9, 20, and 35-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. (^{19}F NMR Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)) in view of Brown (US 817,474) and in further view of Fesik et al. (US 5,989,827) for reason of record.

11. Claims 24 and25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. (^{19}F NMR Measurements of the Rotational Mobility of Proteins in Vivo, Biophysical Journal, 72: 490-498 (January 1997)) in view of Adams et al. (US 5,378,620) for reason of record.

Response to Arguments

12. Applicant's arguments filed 9/2/03 have been fully considered but they are not persuasive.

A) Applicant argues that Williams et al. does not teach or suggest all the claimed elements of the instant invention. Applicant specifically argues that Williams does not teach in vivo determination of structural information about a macromolecule. According to Applicant, Williams et al. only discloses determination of rotational mobility

characteristics or tumbling of a macromolecule, rather structural information about the macromolecule.

In response, it is noted that the feature upon which applicant relies (i.e., in vivo determination of structural information) is not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, the recitation of "structural information" does not appear to exclude Williams teaching of "rotational mobility characteristics or tumbling of a macromolecule"; especially that claims 11 and 14 recite, "structural information is a conformational information" and "said structural information is for a first ... and a second conformation for said selected macromolecule", respectively.

B) Applicant argues that the Williams invention differs in the type of NMR methods employed. Applicant specifically argues that the claimed invention determined in vivo structural information about a macromolecule through the use of multidimensional NMR methods whereas Williams determined rotational mobility data through the use of single-dimensional NMR method.

In response, the rejected claims only recite, "a method of extracting structural information from a NMR data set for a selected macromolecule ... comprising: a) contacting ... with radio frequency...; b) collecting radio frequency data ...; and c) analyzing said data set ... from the NMR data set ...". Thus, the rejected claims do not appear to exclude employing single-dimensional NMR method.

C) Applicant argues that Serber et al. cannot serve as a 102(e) reference since Serber is a publication, and not an application for a patent or a patent.

Examiner concurs and has now properly applied Serber et al. as a 102(a) reference. Additionally, an unsigned "Katz" declaration has not been attached in the Paper as Exhibit D.

D) Applicant argues that the combination of Williams with Brown and Fesik et al. and the combination of Williams with Adams et al. do not render obvious the claimed invention. Applicant argues that all of Brown, Fesik et al., and Adams et al. do not remedy the deficiency of Williams which does not teach or suggest Applicant's element of in vivo determination of a structural feature of a macromolecule.

In response, it is noted that the feature upon which applicant relies (i.e., in vivo determination of structural feature of a macromolecule) is not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, the recitation of "structural information" does not appear to exclude Williams teaching of "rotational mobility characteristics or tumbling of a macromolecule"; especially that claims 11 and 14 recite, "structural information is a conformational information" and "said structural information is for a first ... and a second conformation for said selected macromolecule", respectively.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP 1800/1641

Gailene R. Gabel
Patent Examiner
Art Unit 1641
November 17, 2003